New mannopyranoside-based peptidomimetic compounds, useful for treatment or diagnosis of e.g. intestinal, autoimmune or tumor diseases, are selective α4β7-integrin antagonists

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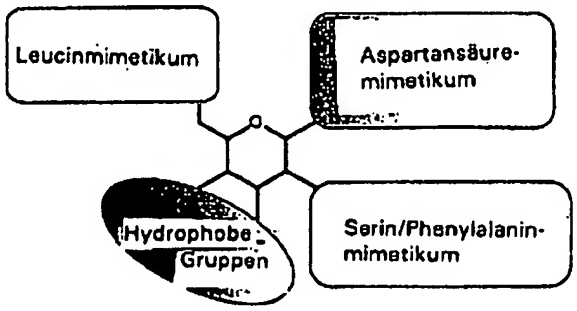
Abstract of **DE10259844**

Mannopyranoside-based peptidomimetic compounds (I) are new. Mannopyranoside-based peptidomimetic compounds of formula (I) are new. X = O or CHR15; R1-R5, R15 = 1-30C organic group optionally containing heteroatoms (specifically O, S and/or N) and optionally substituted (specifically by one or more of NH2, NO2, CN, OH, COOH, C(O)OR6 and/or C(O)NR7R8); R6-R8 = H or 1-10C organic group; Z = linking group with a chain length of two atoms, specifically CH2O, CH2CH2, CH2NH or CH2S). An Independent claim is also included for the preparation of (I) using a biological system.



[0001] The invention concerns new, effective and selective $\alpha_4\beta_7$-Integrin antagonists, that restrain the cell adhesion to the mucosal cell adhesion molecule (MAdCAM-1). The new Integrin antagonists can be used as therapeutic active substances for prevention and treatment of diseases, which are associated with a disturbance by $\alpha_4\beta_7$-integrin cell adhesion at MAdCAM-1 .

[0002] Integrins are heterodimeric transmembrane glycoproteins, which consist of one α - and one β - subunit. They are involved in cell cell and cell matrix interactions (Hynes, Cell 69 (1992), 11-25). 15 different α - and β - subunits are known, and based on current level of knowledge, at least 23 different Integrin receptors can be formed (Eble, Integrin ligand Interaction, Springer Publishing House Heidelberg (1997) 1-40). The family of the Integrin shows substantial differences in their biological functions and ligand specificities.

[0003] The group α 4-Integrins consist of $\alpha_4\beta_7$-Integrin and $\alpha_4\beta_1$-Integrin. Both receptors are expressed on most types by Leucocyte and as Leucocytic receptors and are responsible for both cell cell and cell matrix interactions. The most important endogenous ligands for α_4-Integrin are the vascular cell adhesion molecule-1 (VCAM-1) and Fibronectin (Fn) (Hemler, Annu. Rev. Immunol. 8 (1990), 365-400; Postigo et al., J. Immunol. 151 (1993), 2471-2483) as well as MAdCAM-1, which binds under physiological conditions exclusively at $\alpha_4\beta_7$-Integrin (Berlin et al., Cell 74 (1993), 185-195; Kilger and Holzmann, J. Mol. Med. 73 (1995), 347-354).

[0004] MAdCAM-1 (also called LPAM-1 and $\alpha_4\beta_P$) like VCAM-1 belonged to the Immunglobulin superfamily (IgSF) and possesses three Immunglobulin (Ig) domains. A carbohydrate-rich mucin-like domain is inserted between the second and third Ig domain. The binding of $\alpha_4\beta_7$-Integrin at MAdCAM-1 is obtained mainly by the first N-terminal Ig domain; however sequences from the second Ig domain are also involved. The Leu Asp Thr motive from the N-terminal Ig domain could be identified by Peptide epitope mapping and site specific Mutageneses with MAdCAM-1 as necessary for the binding at $\alpha_4\beta_7$-Integrin (Shroff et al., Bioorg. Med. Chem.Lett. 6 (1996), 2495-2500; Briskin et al., J. Immunol. 156 (1996), 719-726; Viney et al., J. Immunol. 157 (1996), 2488-2497).

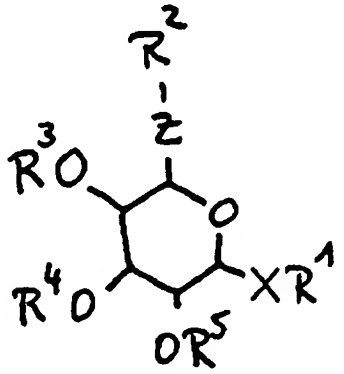
[0005] MAdCAM-1 is the most important counter-receptor for $\alpha_4\beta_7$-Integrin on mucosal endothelial cells (Strauch et al., Int. Immunol. 6 (1994), 236-275). The organ-specific adhesion of normal Lymphocytes and lymphoma cells to endothelial Venules of mesontoric lymph nodes and Peyer's-Flecken marks is obtained by $\alpha_4\beta_7$-Integrin (Holzmann et al., Cell 56 (19891, 37-46; Holzmann and Weissmann, EMBO 8 (1989), 1735-1741; Hu et al., Proc. Natl. Acad. Sci. The USA 89 (1992), 8254-8288). In the mouse model it could be shown that β_7-Integrin and/or MAdCAM-1 block specific anti-bodies recruiting of Lymphocytes in the influence of intestinal fabric and significantly reduce the effect of inflammatory intestine illnesses (Picarella et al., J. Immunol. 158 (1997), 2099-20106). Further anti-bodies against β 7-Integrin (Yang et al., diabetes 46 (1997), 1542-1574) can protect mice from the development of insulin-dependent diabetes.

[0006] Peptidic Integrin inhibitors are well-known. US-A-6,037,324 reveals dipeptide as inhibitors of Integrin-MAdCAM-1-interactions. WO97/25351 reveals peptidic substances with at the N- and C-term bound groups as Mimotope of the conserved motive for amino acid LDTSL of MAdCAM-1. WO98/06248 describes humanised Immunoglobulin with high specificity for Integrin, which exhibit antigen binding region of non-human origin and at least one part of an Immunoglobulin of human origin. US-A-5,510,332 reveals peptides with a length of 4-13 amino acids

encompassing the LDV domain of the CS1-Peptide, which inhibit the binding of $\alpha_4\beta_1$-Integrin at VCAM-1 or fibronectin. US-A-6,087,330 reveals cyclic peptide with 5-13 amino acids derived from the CS1-peptide, which selectively inhibit the binding of $\alpha_4\beta_1$-Integrin at VCAM-1, Fibronectin or Invasin. WO 02/06650 reveals cyclic hexapeptides as peptidomimetics of the conserved amino acid motive for LDTSL with inhibitory effect on the receptor Integrin α4β7-interaction. Inhibitors of the binding of $\alpha_4\beta_1$-Integrin at its receptors, e.g. VCAM-1, are revealed also in US-A-6,096,773. A procedure for the identification of $\alpha_4\beta_7$-antagonist is described in WO00/30681.

[0007] This invention aims at making available new non- peptidic antagonists of α4β7-Integrin which possess in particular a high selectivity for MAdCAM-1. This task is solved by supply of new peptidomimetics on mannopyranosides.

[0008] A the subject of the available invention are thus selective $\alpha_4\beta_7$-integrin-antagonists with the formula (I)



where X represents O or CHR^{15}, in particular O; R^1, R^2, R^3, R^4, R^5 and R^{15} represent independently in each case an organic moiety with 1 to 30 C-atoms, which can contain heteroatoms, in particular selected from O, S and/or N, and/or can be substituted, in particular with one or more substituents selected from NH_2, NO_2, CN, OH, COOH, $COOR^6$ and/or $CONR^7R^8$, where R^6, R^7 and R^8 mean independently in each case H or an organic moiety with 1 to 20 C-atoms to, and Z a group of linkages with a chain length selected by two atoms, in particular - CH_2-O, - CH_2-CH_2, - CH_2-S or - CH_2-NH.

[0009] Surprisingly it was found that the compounds of this invention showed a high and selective inhibitory effect on the interaction of $\alpha_4\beta_7$-Integrin with its receptor, in particular MAdCAM-1.

[0010] Based on a D-Mannose scaffold and/or similar glucoside in particular one β - D-mannose scaffold, selective according to invention antagonists are made available to the similar C-glucoside of it for $\alpha_4\beta_7$-Integrin, in particular for α4β7/MAdCAM-1-interactions.

[0011] The compounds according to invention of the formula (I) are characterised by the fact that they are selective $\alpha_4\beta_7$-Integrin-Antagonists. In contrast to this, many well-known Integrin antagonists molecules interact with α4 and thus are not specific for α4β7 but at the same time are also antagonists for $\alpha_4\beta_1$. Such molecules, which are antagonists for α4-Integrin, are however unsuitable for many applications due to the unwanted binding with $\alpha_4\beta_1$-Integrin. The compounds of this invention concern selective $\alpha_4\beta_7$-Integrin-Antagonist, which means that the binding to $\alpha_4\beta_7$-Integrin is at least double, more preferably triple, still more preferably fivefold and in particular tenfold of the effect on $\alpha_4\beta_1$-Integrin..

[0012] In the compounds of the formula (I) the substituents R^1, R^2, R^3 andR^4 mean an organic substituent with 1 to 20 C-atoms, in particular 1 to 10 C-atoms. The

substituents of R^3 and R^4 are preferably hydrophobic residues, in particular aromatic substituents, in order to increase the hydrophobicityof the peptidomimetics according to the invention. In a particularly preferred embodiment form the substituents of $R^3$and R^4 form together a ring system, whereby the flexibility of the mannose scaffold is limited. In this way the conformation, in which the substituents of R^1, R^2 and R^5 are present, is fixed. The substituent R^1 in particular an Asp substituent (CH_2OOOH) or a mimetic for the Asp substituent. The substituent R^2 particularly represents a substituent derived from Leu (CH_2CH $(CH3)_2$), which is of special importance for the activity of the compounds according to invention. The R^5 is preferably derived from serine (CH_2CH_2OH) or from Phenylalanine ($CH_2C_6H_5$) side chains.

[0013] Z is preferably - CH_2-O or - CH_2-CH_2, in particular - CH_2-O.

[0014] The compounds according to invention are preferably in β - anomeric conformation. In SAR studies (Structure Activity Relationship), it could be stated that Peptidomimetics according to invention with β - orientation of the anomeric center exhibited special activity. It was shown that the cause for the affinity and selectivity for the α4β7/MAdCAM-1-binding is a hydrophobic pocket, which is formed by the substituent at position R^2 and the substituent at position R^5 as well as the conformational rigidity of the mannose scaffold, in particular by cyclization at the positions R^3 and R^4.

[0015] Contrary to well-known Integrin antagonists of the state of the art the selective $\alpha_4\beta_7$-Integrin-Antagonists according to the invention are not peptide compounds. A substantial advantage linked with it is an increased stability and an oral bio-availability. The class of peptidomimetics according to this invention overcomes thereby the disadvantages of peptidic compounds in their application as drugs.

[0016] The invention concerns further compounds with the formula (I) where R^1, R^2, R^3, R^4 and R^5 independently in each case represent an organic substituent with 1 to 30 C-atoms, which can contain, if necessary, heteroatoms, in particular selected from O, S and/or N, which may be substituted, in particular with one or more substituents selected from NH2, NO_2, CN, OH, COOH, $COOR^6$ and/or CONR'RS, where R^6, R^7 and R^8 are independently N or an organic substituent with 1 to 20 C-atoms, and Z a bond or a group of linkages selected from CH_2, O, NH or S.

[0017] Such compounds can be used in particular as selective $\alpha_4\beta_7$-Integrin-antagonist. The compound Carboxymethyl-2-O-benzyl-3,4-O [1 ', 2 ' - dimethoxycyclo-hexan-1',2' diyl - 6-O-isobutyl β - D-mannopyranoside] is particularly preferred.

[0018] Further the invention concerns a pharmaceutical composition, which defines as active substance at least a pyranoside as defined before, if necessary together with pharmaceutical usual carrier, auxiliary or diluents contains. In particular the pyranosides according to invention are used for the production of $\alpha_4\beta_7$-Integrin-Inhibitors, which are useful for the diagnosis, prevention and/or fight against $\alpha_4\beta_7$-Integrin associated diseases, e.g. chronically inflammatory intestine illnesses such as Crohn's disease and Ulcerative Colitis in addition, autoimmune illnesses, in particular asthma, type 1 diabetes and rheumatoid arthritis, transplant rejections, as well as allergies, like e.g. food allergies (Kilger, G., Holzmann, J., J. Mol. Med. 1995, 73, 347 ff.). Further areas of application are radiation and radiotherapy-caused gastro-intestinal tract diseases. In addition, particularly preferred areas of application of the compounds according to invention, are tumors with $\alpha_4\beta_7$-Integrin-participation e.g. metastasis Melanom (Sanders et al., Cancer Invest. 16: 329-44, 1998), non Hodgkin lymphoma, lymphoblastic T-cell lymphoma as well as MALT lymphomas.

Particularly preferred are the uses of the compounds according to invention to the selective inhibition of the effect of $\alpha_4\beta_7$-Integrin with MAdCAM-1, whereby for this purpose particularly such compounds are used, which have inhibitory effect between $\alpha_4\beta_7$-Integrin and MAdCAM-1 at least around the factor 2 higher than concerning the effect on $\alpha_4\beta_1$-Integrin and VCAM-1.

[0019] Still a further object of the invention is a procedure for the inhibition of a $\alpha_4\beta_7$-Integrin, whereby one administers in a pyranoside according to invention in an effective dose into $\alpha_4\beta_7$-Integrin containing biological system, for example a cell or an organism. The procedure according to the invention covers also the administration of the active substance to a needy subject, in particular a human patient.

[0020] The pharmaceutical compositions according to invention can be present in arbitrary form, for example as tablets, as coated tablets or in the form of solutions or suspensions in aqueous or non-aqueous solvents. The compounds are given preferably orally or parenterally in a liquid or solid form. With administration in liquid form water is preferably used as carrier medium, which if necessary contains stabilizers, solubility mediators and/or buffers, which are usually used for injection solutions. Such additives are for example tartrate or borate buffer, ethanol, dimethylsulfoxide, complexing agents as for instance EDTA, polymers as for instance liquid polyethylenglycol, etc.

[0021] With administration in solid form can be used solid supports as for instance starch, lactose, mannitol, methyl cellulose, talcum powder, highly dispersed silicon oxide, high-molecular fatty acids as for instance stearic acid, gel, agar, calcium phosphate, magnesium stearate, animal or vegetable fats or solid high-molecular polymers as for instance polyethylene glycols. Further the formulations can for oral application, if desired, also flavour and sweetener.

[0022] The compounds according to invention can be present also in complexes, e.g. with cyclodextrin as for instance α, β or γ- cyclodextrin.

[0023] For therapeutic uses the given dose depends on the age, state of health and weight of the patient, of the kind of illness, on the kind of the treatment, on the frequency of the administration and the kind of the desired effect. The daily dose of the active connection is usually 0.01 to 50 mg/kg body weight. Normally 0.1 to 40 is and preferably 0.5 to 20 mg/kg/day in one or more doses sufficient, in order to obtain the desired effects.

[0024] The invention concerns further a procedure for the inhibition of $\alpha_4\beta_7$-Integrin, whereby one brings in particular one compound described above in effective dose into an $\alpha_4\beta_7$-Integrin containing biological system, for example a cell or an organism. The procedure can be accomplished both in vivo and in vitro.

[0025] Further the invention is to be described in following described figures and examples.

[0026] Fig. 1 shows schematically the structure of the compounds according to invention.

[0027] Fig. 2 shows IC_{50} measured for

A) a reference compound ($\alpha_4\beta_7$-Antagonist) opposite $\alpha_4\beta_7$/MAdCAM-1-interactions (H.N. Shroff, C.F. Schesender, A.D. Baxter, F. Brookfield, L.J. Payne, N.A. Cochran, D.L. Gallant, M.J. Briskin, Bioorg. Med. Chem.Lett. 1998, 8, 1601)

B) of a reference substance ($\alpha_4\beta_1$-Antagonist) opposite $\alpha_4\beta_1$/VCAM-interaction (J.H. Wang, R.B. Pepinsky, T. Stehle, J.H. Liu, M. Karpusas, B. Browning, L. Osborn, Proc. Natl. Acad. Sci. The USA 1995, 92, 5714) and

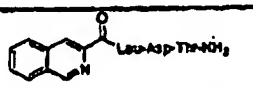
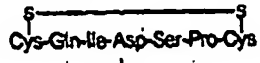
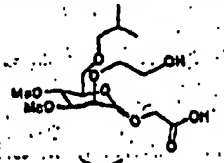
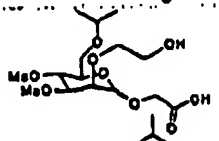
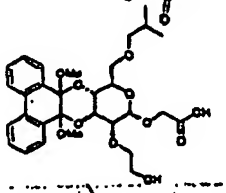
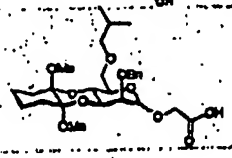
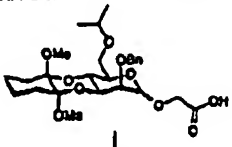
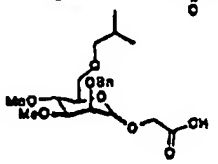
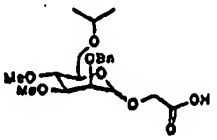
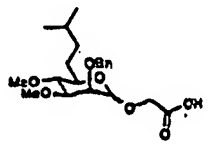
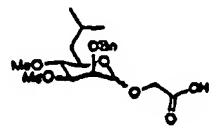
C) of the connection according to invention 20-β on sugar basis opposite $\alpha_4\beta_7$/MAdCAM-interactions.

[0028] Fig. 3 shows the NOESY spectrum, taken up for 20-β in CD_3CN with 275 K. Long-range interactions of the aromatic protons of Phe are marked.
[0029] Fig. 4 shows the overlay of representative structures for 20-β for each of the five clusters determined by molecular modelling.
[0030] Fig.5 shows in Scheme 1 the production of mannose derivatives according to invention as follows:
a) BnBr, KOH in DMSO, 75-85%; b) iBuBr or iPrI, KOH in DMSO, 90-95%; c) 90% TFA in DCM, 80% D) MeI, KOH in DMSO, 70% e) Br_2 in DCM with 0°C f) $HOCH_2CH_2$ (OMe) 2, Ag_2CO_3 in DCM with 0°C, 75%, α/β 1:5 g) N-iodosuccinimide, AgOTf in DCM with 0°C, 80%, α/β 6:1 h) H_2, Pd/C in MeOH, 98% i) $HOCH_2CH_2OBn$, KOH in DMSO, 95% l) HCl in H_2O/THF m) $NaClO_2$, 2-Methyl-2-buten in tert-BuON n) H2, Pd/C in MeOH, 98%.
[0031] Fig. 6 shows the production of compounds according to invention, in which R^3 and R^4 form a ring, R^9 and R^{10} as well as R^{11} and R^{12} forms a further cyclic system according to Scheme 2. Scheme 2 shows: a) TBDPSCl, imidazol in DMF, 85% b) BnBr, KOH in DMSO, 95% C) TBAF in THF, 96% D) iBuBr, KOH in DMSO, 95% e) Br_2 in DCM with 0°C f) $HOCH_2CH_2OH$, Ag_2CO_3 in DCM/THF with 0°C, 90%, α/β1:1 g) TBDPSCI, Imidazol in DMF, 85% h) H2, Pd/C in MeOH, 98% i) $HOCH_2CH_2OBn$, KOH in DMSO, 95% l) TBAF in THF, 96% m) PySO3, TEA in DCM/DMSO 3:1 n) $NaClO_2$, 2-Methyl-2-buten in tert-BuOH o) H_2, Pd/C in McOH, 98%.
[0032] Fig. 7 shows in Scheme 3 manufacture possibilities for particularly preferential compounds, in which the substituents R^3 and R^4 form a cyclic system. Scheme 3 shows: a) $PySO_3$, TEA in DCM/DMSO 3:1 b) toluene, Δ C) KN [Si $(CH_3)_3$] 2 in toluene with 0°C, 70% for 24 E/Z > 1:10 D) $TosNHNH_2$, NaOAc in DME with 80°C, 60-65% e) H2 Pd/C, TEA in MeOH, 80% f) 90% TFA in DCM, 80% g) MeI, KOH in DMSO, 90% h) NBS, HCl in ACN/H_2O, 90-95% i) $SOCl_2$ l) $HOCH_2OOOMe$, Ag_2CO_3 in DCM with 0°C, 75%, α/β 1:5 m) NIS, AgOTf in DCM with 0°C, 80%, α/β 6:1 n) NaOH in McOH/H_2O, 99%.

EXAMPLES

Example 1
[0033] in accordance with into the Fig. 5 to Fig. 7 represented patterns 1 to 3 were manufactured different connections on man eye basis. The inhibition of 38-β_7 ($\alpha_4\beta_7^-$, $\alpha_4\beta_7^+$) cell adhesion at MAdCAM-1 in presence of 1 mg/ml the connections is represented in Table 1.

Table 1. Effects of Peptidomimetics on mannose scaffold on the compound of 38-β_7-lymphoma and Jurkat-Zellen cells to immobilized VCAM-1 and/or. MAdCAM-1.

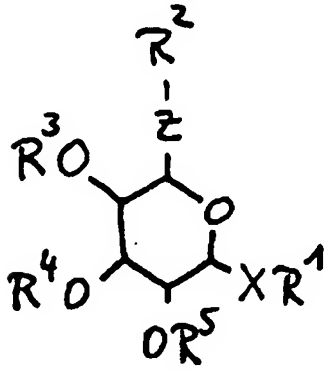
		38-β7 (α4β7) MAdCAM-1 Adhesion [%][a]	Jurkat (α4β1) VCAM-1 Adhesion [%]
Ref.[b] α4β7		10	10
Ref.[c] α4β1		n.d.	52
11- β[d]		100	60
α		100	100
12- β		100	100
α		100	98
19- β		80	82
α		76	81
20- β		15	77
α		90	89
21- β		76	100
α		100	100
22- β		100	86
α		100	100
23- β		100	86
α		100	92
32- β		100	100
α		100	97
33- β		100	100
α		100	100

[a] H.N. Shroff, C.F. Schesender, A.D. Baxter, F. Brookfield, L.J. Payne, N.A. Cochran, D.L. Gallant, M.J. Briskin, Biorg. Med. Chem. Lett. 1998, 8, 1601.
[b] J.H. Wang, R.B. Pepinsky, T. Steal, J.H. Liu, M. Kaprusas, B. Browning, L. Osborn, Proc. Natl. Acad. Sci. The USA 1995, 92, 5714
[c]. Papageorgiou, R. Haltiner, C. Bruns, T.J. Petcher, Bioorg. Med. Chem. Lett. 1992, 2, 135.

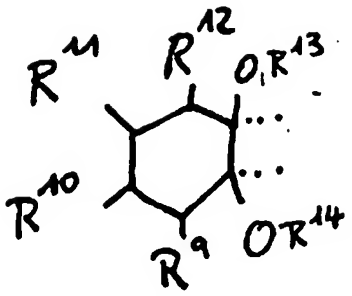
[0034] In addition to the biological activity, selectivity is an important characteristic for the development of drugs. To confirm selectivity, i.e. the ability of the compounds according to invention specific inhibitory effects of Integrin with appropriate ligands was examined the binding of the structurally related integrins $\alpha_4\beta_1$ at VCAM-1. The $\alpha_4\beta_1$-Integrin-mediated adhesion was determined using Jurkat ($\alpha_4\beta_7^+$, $\alpha_4\beta_7^-$) - lymphoma cells. The results are represented in Fig. 2.
[0035] The figure according to invention 20-β showed an inhibition effect in relation to the $\alpha_4\beta_7$/MAdCAM interaction with a IC_{50} of 420 [mu] M (see figure 2).

Claims

1.Selective $\alpha_4\beta_7$-Integrin-Antagonists with the formula (I)



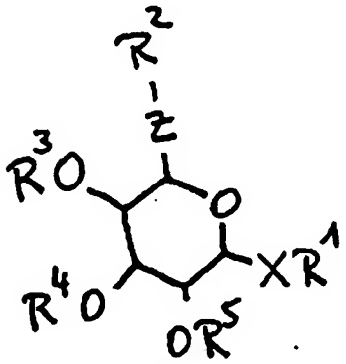
where X represents O or CHR^{15}, R^1, R^2, R^3, R^4, R^5 and R^{15} independently in each case an organic substituent with 1 to 30 C-atoms, which can contain heteroatoms, in particular selected from O, S and/or N and; and/or is substituted in particular with one or more substituents selected from NH2, NO2, CN, OH, COOH, $COOR^6$ and/or $CONR^7R^8$,
where R^6, R^7 and R^8 represent independently in each case N or an organic substituent with 1 to 20 C-atoms and
Z represents a chain length of two atoms, in particular selected from – CH_2-O, - CH_2-CH_2, - CH_2-NH or - CH_2-S.
2. Selective $\alpha_4\beta_7$-Integrin-Antagonists according to claim 1, characterized by the fact that β - anomeric conformation is present.
3. Selective $\alpha_4\beta_7$-Integrin-Antagonisten according to claim 1 or 2, characterized by the fact that R^3 and R^4 form together a ring system.
4. Selective $\alpha_4\beta_7$-Integrin-Antagonisten according to claim 3, where R^3 and R^4 together a ring system of the formula (II)



form, where R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently in each case represent hydrogen or an organic substituent with 1 to 20 C-atoms, whereby two or more of R^9, R^{10}, R^{11} and R^{12} can form ring systems and R^{13} and R^{14} are in particular selected from H, CH_3 and C_2H_5.

5. Selective $\alpha_4\beta_7$-Integrin-antagonists according to one of the preceding claims, characterized by the fact that R^1 represents CH_2OOOH, R^2 represents $CH_2CH(CH_3)_2$ and/or R^5 represents CH_2-C_6H_5 or CH_2CH_2OH.

6. Compounds of the formula (I)



where X represents O or CHR^{15}, and R^1, R^2, R^3, R^4, R^5 and R^{15} independently in each case represent an organic substituent with 1 to 30 C-atoms, which can contain heteroatoms, in particular selected from O, S and/or N which can be substituted in particular with one or more substituents selected from NH_2, NO_2, CN, OH, COOH, $COOR^6$ and/or $CONR^7R^8$,

where R^6, R^7 and R^8 independently in each case represent H or an organic substituent with 1 to 20 C-atoms and

Z represents a chain of two atoms, in particular selected out - CH_2-O, - CH_2-CH_2, - CH_2-NH or - CH_2-S.

7. The compound Carboxymethyl-2-O-benzyl-3,4-O [1 ', 2 ' - dimethoxycyclo-hexan-1',2' diyl] - 6-O-isobutyl β-D-mannopyranoside.

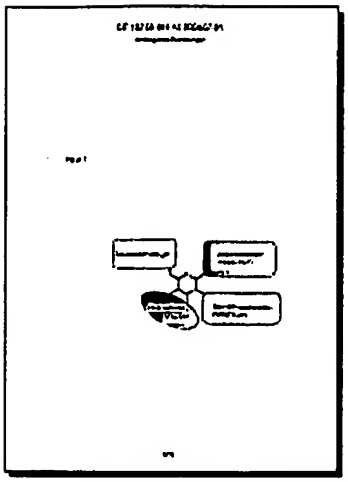
8. Use of a compound of the formula (I) as defined in one of the claims 1 to 7 as $\alpha_4\beta_7$-integrin-antagonist.

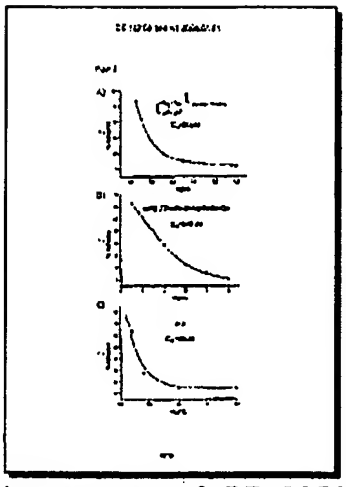
9. Pharmaceutical composition containing selective $\alpha_4\beta_7$-Integrin-Antagonists according one of the claims 1 to 5 or a compound according to claim 6 or 7, if necessary together with pharmaceutical compatible carrier, auxiliary and/or diluents.

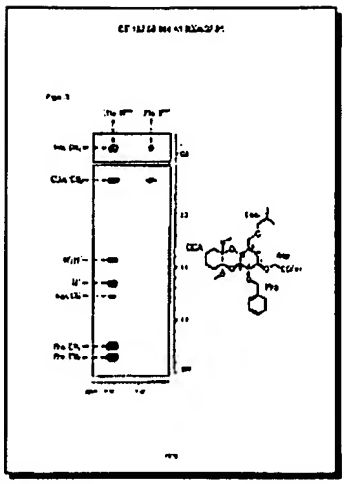
10. Use of selective $\alpha_4\beta_7$-Integrin-antagonists according one of the claims 1 to 5 or a compound according to claims 6 or 7 for the production $\alpha_4\beta_7$-Integrin-Inhibitors.

11. Use according to claim 10 for the production of an inhibitor, which is selective for the interaction between $\alpha_4\beta_7$-Integrin and MAdCAM-1.

12. Use according to claim 10 or 11 for the inhibition of $\alpha_4\beta_7$-Integrin-mediated cell cell or cell matrix interactions.
13. Use of selective $\alpha_4\beta_7$-Integrin-Antagonist according to any one of the claims 1 to 5 or a compound according to claim 6 or 7 for the production of a drug for the diagnosis, prevention and/or therapy of illnesses, which are associated with $\alpha_4\beta_7$-Integrins.
14. Use according to claim 13 for the production of a drug for the diagnosis, prevention and/or therapy of intestine illnesses, in particular Crohn's disease and Ulcerative Colitis or autoimmune illnesses, in particular asthma, diabetes or rheumatoid arthritis.
15. Use according to claim 13 for the production of a drug for the diagnosis, prevention and/or therapy of tumors, in particular metastatic melanoma, Non Hodgkin lymphoma, lymphoblastic T-cell lymphoma or MALT lymphoma.
16. Method for the inhibition of $\alpha_4\beta_7$-Integrinen, characterized by the fact that one administers a compound with formula (I) in accordance with one of the claims 1 to 7 into a $\alpha_4\beta_7$-Integrin containing biological system.







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